AMENDMENTS

In the Claims

Please cancel claims 5, 7, 10-13, 18-21, 24, 27-35, 37 and 39 without prejudice, these claims being drawn to a non-elected invention.

Please amend claims 1, 6, 8-9, 14, 17, 22-23, 25-26, 36 and 38 as follows:

1. (Twice Amended) A method of producing a biologically active anti-angiogenic protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising:

   (a) inserting an isolated polynucleotide sequence encoding a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, into a yeast expression vector, wherein the vector contains a multiple cloning site; and

   (b) transforming an appropriate yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein, or the biologically active anti-angiogenic mutant, fragment or fusion protein thereof;

   thereby producing a biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof.

6. (Twice Amended) The method of Claim 1 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

8. (Twice Amended) The method of Claim 1 wherein the isolated polynucleotide of step (a) additionally comprises a polynucleotide linker, and the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant,

fragment or fusion protein thereof produced in step (b) additionally comprises at least one amino acid residue resulting from the polynucleotide linker.

9. (Twice Amended) The method of Claim 8 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof produced comprises two additional amino-terminus amino acid residues.

14. (Twice Amended) The method of Claim 1 wherein the vector of step (a) comprises a pPICzαA plasmid wherein the plasmid contains a multiple cloning site, said cloning site comprising a His.Tag motif and wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof produced in step (b) comprises a histidine tag motif.

17. (Twice Amended) The method of Claim 14 wherein the biologically active anti-angiogenic restin protein, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof is produced at a concentration of 10-20 milligrams or more per liter of culture fluid.

22. (Twice Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide sequence encoding a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector

comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein or biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising at least one amino acid residue resulting from the linker polynucleotide;

thereby producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof.

23. (Twice Amended) The method of Claim 22 wherein the polynucleotide additionally encodes angiostatin, endostatin, or mutants, fragments or fusion proteins thereof.

25. (Twice Amended) A method of producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide sequence encoding a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker and wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin protein or biologically active

anti-angiogenic mutant, fragment or fusion protein thereof comprising at least one amino acid residue resulting from the linker polynucleotide, and wherein the protein or mutant, fragment or fusion protein thereof additionally comprises a histidine tag motif;

thereby producing a biologically active anti-angiogenic restin protein, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof.

26. (Twice Amended) The method of Claim 25 wherein the polynucleotide additionally encodes endostatin, angiostatin, or mutants, fragments or fusion proteins thereof.

36. (Amended) A method of producing biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising:

(a) inserting an isolated polynucleotide sequence encoding a biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the polynucleotide linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin or biologically active anti-angiogenic mutant, fragment or fusion protein thereof, comprising at least one amino acid residue resulting from the linker polynucleotide;

thereby producing a biologically active anti-angiogenic restin, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof.

38. (Amended) A method of producing biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment or fusion protein] thereof, comprising:

(a) inserting an isolated polynucleotide sequence encoding a biologically active anti-angiogenic restin, or a biologically active anti-angiogenic mutant, fragment or fusion protein thereof, wherein the polynucleotide additionally comprises a linker, wherein the linker encodes at least one amino acid, into a yeast expression vector comprising a pPICzαA plasmid wherein the plasmid contains a multiple cloning site and wherein the cloning site additionally comprises a histidine tag motif; and

(b) transforming a *Pichia pastoris* yeast strain with the vector of step (a) and maintaining the yeast strain under suitable conditions for the production of the biologically active anti-angiogenic restin or biologically active anti-angiogenic mutant, fragment or fusion protein thereof wherein the protein or mutant, fragment or fusion protein comprises at least one amino acid residue resulting from the linker polynucleotide and a histidine tag motif;

thereby producing a biologically active anti-angiogenic restin, or biologically active anti-angiogenic mutant, fragment or fusion protein thereof.

Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - vi).

REMARKS

Claims 1-4, 6, 8-9, 14-17, 22-23, 25-26, 36 and 38 are currently pending in the application. Claims 5, 7, 10-13, 18-21, 24, 27-35, 37 and 39 are canceled. Claims 1, 6, 8-9, 14, 17, 22-23, 25-26, 36 and 38 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.